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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,642	12/22/2000	Thomas B. Albrecht	026.00041	4973

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EXAMINER	
LACOURCIERE, KAREN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,642	ALBRECHT ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8, 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6-16-03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03-22-2004 has been entered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4-6 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting replication and infection of human cytomegalovirus using a calpain inhibitor, does not reasonably provide enablement for methods of inhibiting replication and infection of herpes simplex virus or varicellar zoster virus using a calpain inhbitor.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 6-8 and 14-16 are drawn to inhibiting the replication of decreasing viral replication treating viral infection in an individual by administering a calpain inhibitor wherein the viral replication or infection is caused by human cytomegalovirus, herpes simplex virus or varicellar zoster virus.

The specification discloses methods wherein the calpain inhibitors E64D and Z-Leu-Leu-H are administered to HCMV infected cells in vitro, which results in an inhibition of the degradation of $p21^{cip1}$ in those cells relative to untreated HCMV infected cells. The specification indicates that decreases in $p21^{cip1}$ activate E kinase which is critical for efficient HCMV replication. The Art of record (Chen et al. J. Virol. 2001, cited on PTO form 1449, filed June 16, 2003) indicates that treatment with a calpain inhibitor Z-Leu-Leu-H causes a 99.7% decrease in viral infectivity (see for example, p3622, 2^{nd} column). The specification does not demonstrate any correlation between a calpain inhibitor and any activities associated with herpes simplex virus or varicellar zoster virus,

either in vitro or in vivo, nor does it demonstrate any correlation between the effects demonstrated with HCMV and either herpes simplex virus or varicellar zoster virus. Neither the prior art, nor the specification indicate any involvement of calpain in herpes simplex virus or varicellar zoster virus replication or infection.

At the time of the instant invention, and even to date, methods of treatment for viral infections were unpredictable, and the life cycle of many viruses were unknown or not well defined, including the specifically claimed viruses, human cytomegalovirus, herpes simplex virus or varicellar zoster virus. The art of the field of viral infections did not suggest that calpain, or anything else inhibited by a calpain inhibitor is associated with viral replication or infection for herpes simplex virus or varicellar zoster virus. The art demonstrates that inhibition of calpain does not necessarily cause inhibition of replication generally for viruses. For example, Debaisi et al. (reference 8 on PTO form 1449, filed July 19, 2002) demonstrates that calpain inhibitors act independent of reovirus replication (see abstract, for example). Although the claims are not directed to reovirus, the results of Debaisi et al. would suggest that even though HCMV replication and infectivity may be decreased with calpain inhibitors, the skilled artisan would not expect this inhibition to correlate generally for other viruses, including herpes simplex virus or varicellar zoster virus. Additionally, Debaisi et al. disclose that calpain may be involved in many physiological roles in a viral infected cell, but that further research would be required before a potential therapeutic intervention can be developed (see for example, p 699). The instant specification does not provide sufficient information regarding herpes simplex

virus or varicellar zoster virus infections, such that the skilled artisan would be able to practice the methods claimed. In order to practice the scope of the claimed methods, one skilled in the art would need to undergo undue trial and error experimentation to determine whether herpes simplex virus or varicellar zoster virus replication can be reduced or infections can be treated using a calpain inhibitor and how to treat such a viral infection in an individual. Even for the specific embodiments claimed, it is unclear that there is any correlation between calpain inhibitors and viral replication and infection. Given the unpredictability of the treatment of viral infections, as well as the unknown and unpredictable role of calpain in viral infections, including those specifically claimed, it is unpredictable that inhibitors of calpain would have any effect on the replication or infection of herpes simplex virus or varicellar zoster virus. The skilled artisan would not expect the results for human cytomegalovirus to correlate for any other virus, including herpes simplex virus or varicellar zoster virus. Given the complex nature of viral infections, including herpes simplex virus or varicellar zoster virus, and the difficulty in determining effective treatments, even through this undue trial and error experimentation, the skilled artisan may never be successful.

Therefore, at the time of the instant invention, one skilled in the art would not have been able to practice the claimed invention over the full scope claimed without undue trial and error experimentation.

Response to Arguments

Applicant's arguments filed 12-18, 2003 have been fully considered but they are not persuasive. In the After final amendment filed 12-18-2003, Applicant argues that the claims are enabled because the specification sets forth the steps necessary to practice the claimed methods, wherein cells are contacted with a DNA virus and then contacted with a calpain inhibitor. Applicant argues that the specification demonstrates calpain inhibitors protect $p21^{cip1}$, which results in a decrease in activation of E kinase, which is essential for HCMV viral replication. Applicant further argues that treating virally infected cells with an inhibitor of cellular proteases and the measurement of the resultant viral infection is known as well as testing for the reduction in activity of proteases such as calpain is known. Applicant argues that some experimentation does not indicate a lack of enablement as long as the experimentation is not undue.

These arguments have been considered to the extent that they read on the instant rejection, but have not been found persuasive.

The specification does not provide methods that correlate reasonably with the full scope of the claimed methods. For example, the specification only provides methods using HCMV, which, as discussed in the rejection of record, would not be expected to predictably correlate with methods for herpes simplex virus or varicellar zoster virus. Further, although administration of protease inhibitors were known in the art and methods for measuring viral replication were known, these arguments do not address the methods claimed. For example, the

methods claimed are not directed to measuring the level of viral replication, rather to inhibition of viral replication. Being able to measure the potential outcome, or lack thereof, of a method does not enable the method. Determining viral levels does not address in vivo methods of treatment, as encompassed in the claims. The claimed methods are unpredictable, as discussed in the rejection of record, and the methods disclosed would not be predicted to correlate with methods for other viruses, including herpes simplex virus and varicellar zoster virus, and the specification has not enabled the full scope of the claimed methods.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
June 9, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER